Exhibit B

EXPERT REPORT OF DEBRA L. FROMER, M.D.
TVT Obturator General Report

I have prepared this Expert Report in the matter of In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, MDL No. 2327, currently pending in the United States District Court for the Southern District of West Virginia, before the Hon. Joseph R. Goodwin My opinions set forth in this report are made to a reasonable degree of medical certainty, and are based on information and knowledge I have acquired from my education, training, personal experience in private practice, teaching, research, discussion and interaction with other pelvic surgeons in professional activities and conferences, and review of medical literature and records.

BACKGROUND AND QUALIFICATIONS

I am the Chief of Female Pelvic Medicine and Reconstructive Surgery at Hackensack University Medical Center, the Program Director for the Fellowship in Female Pelvic Medicine and Reconstructive Surgery at Hackensack University Medical Center, and Assistant Professor in Urology at Rutgers, the State University of New Jersey.

I received my Bachelor of Arts degree in Anthropology at the University of Pennsylvania, graduating Magna Cum Laude. Following my undergraduate education, I attended Tufts University School of Medicine and graduated with honors (Alpha Omega Alpha) in 1998. I completed my general surgical training in 1999 at Columbia Presbyterian Medical Center, where I stayed to complete my training in Urology in 2003. I subsequently joined the faculty practice at Hackensack University Medical Center where I have been practicing for the last 11 years. Over this time, I have cultivated a largely female urology practice, having been the only woman practicing adult urology in Northern New Jersey. Female patients make up approximately 90% of my practice. As such, my practice has largely become focused on female pelvic medicine and reconstructive surgery with high volumes of women seeking treatment for conditions such as urinary incontinence, prolapse, recurrent urinary tract infection, female sexual dysfunction, and pelvic pain. I am a frequently invited lecturer at medical and surgical conferences addressing urinary incontinence, the surgical management of prolapse and incontinence, and the treatment of overactive bladder. I am Board-certified in both Urology and in Female Pelvic Medicine and Reconstructive Surgery. I have performed over 1,000 anti-incontinence procedures, the vast majority of which consisted of polypropylene mesh slings.

As an Associate Professor at Rutgers New Jersey Medical School and as Fellowship Director for our Female Pelvic Medicine and Reconstructive Surgery program, I am actively involved in training urology residents from Rutgers New Jersey Medical School and from New York Medical College as well as subspecialty training our fellows in Female Pelvic Medicine and Reconstructive Surgery. Many of these individuals go on to practice the techniques that I have taught them in order to deliver safe and effective use of the TVT products.

In addition to training residents and fellows, I also have served as a preceptor for Ethicon in approximately 2012, and our institution has served as a physician training site for Ethicon. During this training, urology and/or gynecology residents, fellows and attendings were instructed on TVT, TVT-O and Prolift. This was accomplished with one to two hours of didactic training and two to four hours of hands-on cadaver training. My involvement in these training programs included preparation, planning and organization of the program, as well as contributing to both the didactic and the hands-on training as a proctor. The fees I have been paid by Ethicon in this regard have been under $5000.

My expert fees in this litigation are $550 per hour for review of medical literature, review of medical records and depositions, preparation of expert reports, and phone calls. For depositions, trial testimony, deposition preparation, and trial testimony preparation, I charge $7500 per full day and $4000 per half-day.

Attached as Exhibit A is a copy of my current *curriculum vitae*, which includes a list of my publications, presentations, awards and other academic accomplishments.

MATERIALS I HAVE REVIEWED

In the course of preparing this report, I have reviewed numerous documents. I have examined the published literature on TVT and TVT-O. I have reviewed professional education materials produced by Ethicon, as well as the Instructions for Use (IFU) of the TVT-O product, TVT patient brochures, the TVT Surgeon Resource Monograph, and various company documents. I have also read the numerous medical society statements and the statement issued by the Food and Drug Administration (FDA) regarding synthetic midurethral slings. A list of the materials that I have reviewed and/or considered in preparing this report is attached as Exhibit B to the report.

DEFINITION OF URINARY INCONTINENCE[1]

Urinary incontinence is defined as the involuntary loss of urine. Different types of urinary incontinence exist:

1. Stress urinary incontinence refers to the symptom of unwanted leakage of urine associated with increases in intra-abdominal pressure that may occur with coughing, sneezing or activities such as lifting, bending, exercise or changing position.

[1] Abrams P, Andersson KE, Birder L, et al: Fourth international consultation on incontinence recommendations of the international scientific committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. Neurourology and Urodynamics 2010, 29:213-240.

2. Urge urinary incontinence is the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency. Urge urinary incontinence is one component of overactive bladder.

3. Mixed Urinary Incontinence is the complaint of involuntary leakage of urine associated with urgency and also with effort, exertion, sneezing and coughing.

4. Nocturnal enuresis is any involuntary loss of urine occurring during sleep.

5. Post-micturition dribble and continuous urinary leakage and continuous urinary leakage denotes other symptomatic forms of incontinence.

EPIDEMIOLOGY AND PSYCHOSOCIAL IMPACT OF URINARY INCONTINENCE

Estimates of the prevalence of urinary incontinence in women vary widely in the medical literature due to differing definitions. Using the inclusive definition of any leakage of urine at least once in the past year, prevalence ranges from 25% to 51%.[2] A large meta-analysis reported an estimated prevalence of urinary incontinence of 30% in women aged 30 to 60 years, with half of the cases attributed to stress urinary incontinence.[3]

The prevalence of incontinence increases with age. In a large survey of nonpregnant women in the United States, moderate or severe urinary incontinence affected 7% of women ages 20 to 39, 17% of women ages 40 to 59, 23% of women ages 0 to 79, and 32% of women age 80 and over.[4]

There is a large body of literature demonstrating the potential of urinary incontinence to hinder aspects of daily living, thereby negatively impacting quality of life. Up to 23% of women take time off from work due to their incontinence, between 25% to 50% of women with urinary incontinence suffer from sexual dysfunction, and urinary incontinence can commonly leave the sufferer with psychological morbidity, particularly depression.[5]

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[2] Buckley BS, Lapitan MC: Epidemiology Committee of the Fourth International Consultation on Incontinence, Paris 2008. Prevalence of urinary incontinence in men, women, and children—current evidence: findings of the Fourth International Consultation on Incontinence. Urology 2010; 76:254. Markland AD, Richter HE, Fwu CW, et al: Prevalence and trends of urinary incontinence in adults in the United States, 2001 to 2008. J. Urol. 2011; 186:589.

[3] Hampel C, Weinhold D, Benken N et al: Definition of overactive bladder and epidemiology of urinary incontinence. Urology 1997; 50:4.

[4] Nygaard I, Barber MD, Burgio KL, et al: Prevalence of symptomatic pelvic floor disorders in US women. JAMA 2008; 300:1311.

[5] Sinclair AJ and Ramsay IN: The psychosocial impact of urinary incontinence in women. The Obstetrician and Gynecologist 2011;13:143-148; Coyne KS, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR: Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom and the United States. Eur Urol 2012; 61:1: 88-95.

ETIOLOGY OF URINARY INCONTINENCE[6]

During bladder filling, bladder muscle activity is normally suppressed by brain-mediated reflexes. The bladder outlet and urethra must be closed at rest and during periods of increased abdominal pressure in order to maintain continence. With rare exceptions, urinary incontinence occurs when the pressure within the bladder exceeds the pressure required by the urethral sphincter to maintain continence. When the urethral resistance is unable to maintain this pressure, urine can flow involuntarily past the urethral sphincter, resulting in unwanted leakage of urine.

Urinary incontinence can result from abnormalities of the urethra or the bladder, or a combination of both of these structures. These abnormalities can be the result of overfunction of the bladder, underfunction of the bladder, or underfunction of the urethra. Stress incontinence refers to urinary incontinence that occurs as a result of a poorly functioning urethra, usually in the setting of rises in intra-abdominal pressure, which result from activities such as coughing, sneezing, and activity. Many factors contribute to the maintenance of urethral incontinence. These include passive urethral closure (maintained by mucosal "seal," muscle fibers, and connective tissue), a critical urethral length, preservation of the normal anatomic position of the bladder neck and urethra, and adaptive changes that may occur during moments of increased abdominal pressure. Identifiable risk factors for the development of SUI include pregnancy, childbirth, menopause, cognitive impairment, obesity and advanced age.

DIAGNOSIS AND EVALUATION OF URINARY INCONTINENCE[7]

Patient history, physical examination and basic testing can diagnose patients with urinary incontinence in most straightforward cases. When taking a patient's history, particular emphasis should be placed upon ascertaining the presence, severity, duration and bother of any urinary, bowel or prolapse symptoms, the effect of the symptoms on a patient's quality of life, and the presence of symptoms suggesting neurological disease. Coexisting diseases, patient medications, physical impairments, obstetrical and menstrual history, and previous genitourinary or bowel surgery may all play a role in contributing to the patient's incontinence. The components of the physical examination in diagnosing urinary incontinence include assessing the patient's general status (mental status, obesity, mobility), abdominal examination, pelvic examination and neurological examination. On physical examination, assessments of urethral mobility, urethral pathology, pelvic floor strength, and pelvic support compartments should be made. Furthermore, urinalysis can detect a potential urinary tract infection which could be an easily treatable cause of urinary incontinence. Further assessments with bladder diaries to document the frequency and quality of incontinence episodes, validated questionnaires, measurements of post void residual urine volumes, urodynamic testing, imaging of the urinary tract and endoscopy may be indicated based on the complexity of the patient's status.

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[6] Rovner ES and Wein AJ: Treatment options for stress urinary incontinence. Rev Urol (2004): 6(Suppl 3): S29-S47.

[7] 5th ICI; ACOG/AUGS Committee Opinion June 2014.

MANAGEMENT OF OVERACTIVE BLADDER AND URGE URINARY INCONTINENCE

There are a wide variety of options for the management of urge incontinence and overactive bladder in the patient with either isolated urge urinary incontinence or in the patient with mixed urinary incontinence. An update on the AUA Guidelines on the management of overactive bladder and urge urinary incontinence was presented at the national meeting of the American Urological Association in May 2014.[8] These guidelines divide the plethora of nonsurgical and minimally invasive treatments into three tiers of therapy:

First Line Therapy: Behavioral Therapy

Clinicians should offer patients with overactive bladder and urge incontinence behavioral therapy that includes pelvic floor muscle training, bladder control strategies, bladder retraining, and fluid management. Practitioners and patients are encouraged to persist with behavioral therapies for 8 to 12 weeks. These therapies may be combined with pharmacotherapy as well.

Second Line Therapy: Pharmacotherapy

There are a multitude of medications available for the treatment of overactive bladder and urge incontinence which are safe, effective and generally well-tolerated in the vast majority of patients. Medications include anti-muscarinic agents such as oxybutynin, tolterodine, darifenicin, solifenacin, trospium, and fesoterodine. In addition, beta-agonist therapy (mirabegron) may be utilized as a newer alternative to anti-muscarinics. Patients and practitioners are encouraged to persist with pharmacological therapy for 4 to 8 weeks.

Third Line Therapy

If behavioral therapy and pharmacotherapy fail, either due to lack of efficacy or lack of tolerability, a variety of minimally invasive treatment options can be offered. Onabonulinum toxin A (Botox) has been proven to be a safe and highly effective treatment option for the patient with refractory overactive bladder. This therapy can be delivered in the doctor's office under local anesthesia. A total of 27 recent studies with 887 patients showed that with 100 units of Botox, there were sustained improvements in urge incontinence, frequency, nocturia, pad use and quality of life. Percutaneous tibial nerve stimulation (PTNS) is another treatment that can be performed in the doctor's office. This therapy involved the placement of a small acupuncture-like needle into the tibial nerve, located behind the ankle. A gentle electrical stimulus is applied to the nerve for 30 minutes, once per week for a total of 12 weeks. Success rates range from 60 to

[8] Gormley EA et al: Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guidline. Presented at AUA National meeting May 2014.

70%. Should all treatment options fail, patients can be offered sacral nerve stimulation with the placement of a "bladder pacemaker" under sedation in the operating room. This therapy can be up to 80% successful in the management of overactive bladder and urge urinary incontinence.

NON-SURGICAL MANAGEMENT OF STRESS URINARY INCONTINENCE (SUI)

Behavioral Therapy

Behavioral modifications for the treatment of SUI include patient education, fluid and dietary management, timed and complete voiding, a voiding log and weight loss. Behavioral therapy is usually combined with pelvic floor muscle exercises. Though this form of therapy is simple, inexpensive, and has no significant side effects, behavioral therapy requires patient and caregiver motivation and commitment, as failure to comply with such a program will result in a reduction in efficacy.

Pelvic Floor Muscle Training

Pelvic floor muscle exercises can be performed by the patient alone, or with the assistance of a pelvic floor therapist and/or biofeedback. Short term success rates in terms of reported improvements in continence average at approximately 40% with a 25% continence rate. Longer term studies show similar continence rates, however more women reported worsening of their condition and half of patients were no longer training. Therefore, though pelvic floor muscle exercises show some efficacy and have minimal side effects, longer term studies show poor compliance limiting their use in the long term management of SUI.[9]

Electrical Stimulation

Pelvic floor electrical stimulation involves the application of an electrical current to the pelvic floor via an electrode inserted intravaginally or rectally. There is wide variation in success rates for patients with SUI treated with electrical stimulation. This may be due to a lack of universal agreement on the method of application, the duration of therapy, the amplitude or frequency of impulse, or timing of therapy. [10]

Intravaginal Supportive Devices

Pessaries

Although most commonly used to treat pelvic organ prolapse, pessaries can also be utilized in the nonsurgical management of SUI. A large Cochrane Systematic Review

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[9] Lagro-Janssen T and can Weel C: Long-term effect of treatment of female incontinence in general practice. Br J Gen Pract. 1998; 48(436):1735-8.

[10] Rovner ES and Wein AJ: Treatment options for stress urinary incontinence. Rev Urol. 2004;6 Suppl 3:S29-47.

with 7 trials involving 732 women shows that there is little evidence from controlled trials to judge whether pessary use is better than no treatment at all.[11]

Vaginal Cones

These devices can be inserted into the vagina and maintained in place by active pelvic floor muscle contraction. Vaginal cones are available in a variety of weights, with the patient being instructed to insert progressively heavier cones as the pelvic floor becomes stronger. A large review of 23 trials involving 1806 women showed that vaginal cones are better than no active treatment in women with SUI and may be of similar efficacy to PFMT and electrostimulation.[12]

Continence Devices

Occlusive devices that can be externally or internally applied have been used to treat SUI in women. Very few of these plug-like devices that require intra-urethral insertion are currently available for commercial use in the United States due to voluntary withdrawal from the market.[13]

New Over The Counter Occlusive Vaginal Devices

More recently, a company that makes pads for the management of urinary incontinence has released a tampon-like device for the treatment of stress incontinence that appears to function similarly to a pessary. There is limited if any research on this new product.

Pharmacological Therapy

Although certain medications aimed at increasing bladder outlet resistance have been theorized to have efficacy in the treatment of SUI, published studies lack objective evidence of successful management of SUI.

SURGICAL TREATMENT OF SUI (AUA GUIDELINES)

Retropubic Suspensions

Retropubic suspension surgery (MMK, Burch, paravaginal repair) treats SUI by elevating the bladder neck into an intra-abdominal position with sutures. Such anatomic position allows normal pressure transmission during periods of increased intra-abdominal pressure. Retropubic suspension is abdominal surgery performed under general anesthesia, whereby access to the bladder and urethra is gained by making an abdominal

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11 Lipp A, Shaw C, Glavind K. Mechanical devices for urinary incontinence in women. Cochrane Database of Systematic Reviews. 2011, Issue 7.

12 Herbison GP and Dean N: Weighted vaginal cones for urinary incontinence. Cochrane Database Syst Rev 2013; 7:CD002114.

13 Elliott DS and Boone TB: Urethral devices for managing stress urinary incontinence. J Endourol, 1000;79-83.

incision. This surgery can be performed through one large incision (open surgery) or through several small incisions (laparoscopic surgery).

The Burch colposuspension is the most common procedure used for retropubic suspension. With this procedure, sutures are used to attach the paravaginal tissue near the bladder neck to Cooper's ligament, a structure next to the pubic bone. According to the AUA Guidelines Panel on the Surgical Management of SUI, their meta-analysis estimated cured/dry rates at 12 to 23 months based on 1,085 patients for open suspensions to be 82%, while cured/dry rates for laparoscopic suspensions were 69%. At 24 to 47 months, the cured/dry rates for all procedures ranged from 74% to 76%. The estimate of post-operative urge incontinence in patients treated with open surgery was 14% in patients with pre-existing urge incontinence. Eight percent and 41% of patients developed *de novo* and "unspecified" urge incontinence, respectively, postoperatively. Retention occurred in 3 to 4% of patients. The most common complications for open retropubic suspensions were fever (8%), urinary tract infection (13%), bladder injury (4%) and voiding dysfunction (9%). Ureteral injury occurred in 4-11% of patients undergoing laparoscopic suspensions.[14]

Injectable Agents

Injectable therapy using bulking agents composed of synthetic materials, bovine collagen, or autologous substances augments the urethral wall and increase urethral resistance to urinary flow.

Evidence in major reviews shows low efficacy rates compared with surgical incontinence therapies, a need for repeat treatments because of symptom recurrence, and problems with the injection of some synthetic agents. Overall, injections of urethral bulking agents can help the group of patients that is unfit or unwilling to undergo surgery for incontinence.[15]

Sling Procedures

These procedures involve placing a band of sling material directly under the bladder neck/proximal urethra or mid-urethra. This material acts as a physical support to prevent bladder neck and urethral descent during physical activity. The sling may also augment the resting urethral closure pressure with increases in intra-abdominal pressure. Slings can be autologous, cadaveric or synthetic.

Autologous fascial slings are constructed from the patient's own tissues, such as the rectus fascia from the lower abdomen or the fascia lata from the thigh. These procedures may require extensive dissection at the site of harvested autologous tissue. The estimated cure/dry rate for these procedures range from 72 to 88% at 24 to 48 months after surgery.[16] The AUA panel's meta-analysis estimated rates of post surgical

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[14] Appell RA, et al: Guideline for the surgical management of female stress urinary incontinence Update (2009)

[15] Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S. Urethral injection therapy for urinary incontinence in women. *Cochrane Database Syst Rev.* 2012;2:CD003881.

[16] Appell RA, et al: Guideline for the surgical management of female stress urinary incontinence Update (2009)

urge incontinence were 33% in patients with pre-existing urge incontinence, and *de novo* urge incontinence in 9% patients without pre-existing urge incontinence. The estimated rate of retention was 8%. Complications included urinary tract infections (11%), bladder injury (4%) and wound complications (8%).[17]

Cadaveric slings came into wide use after a successful report was published in 1996.[18] However, concern over their long-term efficacy began to emerge with reports of graft failure and declining success over time. Based on limited data, estimated efficacy was 74% at 12-24 months and 80% at 24 to 48 months, with a wide range likely due to variability of processing and storing cadaveric materials. Few studies reported data on retention, urge incontinence and complications. [19]

MIDURETHRAL SYNTHETIC SLINGS: HISTORY AND POSITION STATEMENTS

Developed in the late 1990s based on the integral theory of Petros and Umsten,[20] the midurethral sling has become the most commonly performed and most thoroughly evaluated procedure in the surgical management of stress urinary incontinence.[21] There is a plethora of data that demonstrates the efficacy and safety of the midurethral sling as the gold standard for the surgical management of stress urinary incontinence in women. The AUA Guidelines have concluded that the retropubic mid-urethral sling is equally efficacious to the pubovaginal sling with decreased morbidity. [22] The Cochrane review of published literature has reached similar conclusions.[23] The Urinary Incontinence Treatment Network (UITN) completed a multicenter, prospective, randomized trial (TOMUS) between the retropubic mid urethral sling and the transobturator sling, and both procedures were found to be safe and efficacious with an acceptable incidence of adverse events.[24]

Additionally, position statements from SUFU, AUGS, AUA and IUGA support the use of mid-urethral slings as the gold standard for the treatment of stress urinary incontinence in women.[25] [26] [27] In fact, the IUGA position statement stresses that "there is robust evidence to support the use of midurethral sling from over 2,000 publications

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17 Appell RA, et al: Guideline for the surgical management of female stress urinary incontinence Update (2009)

18 Handa VL, Jensen JK, Germain MM et al: Banked human fascia lata for the suburethral sling procedure: a preliminary report. Obstet Gynecol 1996; 88:1045.

19 Carbone JM, Kavaler E, Hu JC et al: Pubovaginal sling using cadaveric fasca and bone anchors: disappointing early results. J Urol 2001; 165: 1605, Fitzgerald MP, Mollenhauer J and Brubaker L: Failure of allograft suburethral slings. BJU Int 1999; 84: 785, O'Reilly KJ and Govier FE: Intermediate failure of pubovaginal slings using cadaveric fascia lata: a case series. J Urol 2002; 167: 1356

20 Petros P and Ulmsten U: An integral theory of female urinary incontinence, Experimental and clinical considerations. Acta Obstet Gynecol Scand, suppl., 1990; 153: 7.

21 Badlani G, Winters JC: AUA News Volume 18, Issue 12, December 2013: 1

22 Appell RA, et al: Guideline for the surgical management of female stress urinary incontinence Update (2009)

23 Ogah J, Cody DJ and Rogerson L: Minimally invasive synthetic suburethral sling operation for SUI in women: a short version Cochrane review. Neurourol Urodyn 2011; 30: 284

24 Richter H, Albo M, Zyczynski H et al: Retropubic versus transobturator midurethral slings for stress urinary incontinence. N Engl J Med 2010; 362: 2066.

25 SUFU position statement on Midurethral Slings for Stress Urinary Incontinence. www.sufuorg.com

26 AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence. www.auanet.org

27 IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence. www.iuga.org

making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use." Similarly, the SUFU/AUGS position statement on mesh slings states that "the polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women." Furthermore, in 2013 the FDA clarified warnings on the usage of transvaginal mesh, concluding that the benefit-to-risk ratio of mid-urethral slings is clearly favorable and did not recommend any alteration of their use. The FDA website states that "the safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year."[28] Furthermore, in November 2015 The American Congress of Obstetrics and Gynecology published a Bulletin stating, "synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colpopsuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colpopsuspension that with synthetic midurethral slings." As is consistent with the opinions of other gynecological, urogynecological and urological societies, as well as my own expert opinion, the ACOG bulletin concluded that there are "substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women."[29]

The first mid-urethral sling procedure, the Gynecare Tension-free Support for Incontinence ("TVT"), manufactured by Ethicon, was developed as a minimally invasive procedure to treat stress urinary incontinence by supporting the midurethral mechanism with a synthetic polypropylene, monofilament tape-like mesh placed by a retropubic, bottom-to-top approach. Initial results showed 91% success at 1 year with a low complication rate that included one bladder perforation and voiding dysfunction in four patients from a cohort of 130 women.[30] Subsequent studies showed long-term success in 85% with a median follow up of 56 months and 90% at 11 years with no long-term adverse events.[31] Now that TVT has been on the market for 17 years, Nilsson et al. published their 17-year data on the success and safety of TVT. A cohort of 90 women who underwent the TVT procedure were followed for 17 years. At the end of this time period, 90% of the women who were available for 17-year follow up were objectively continent, and 87% were subjectively cured or significantly improved. Only one case of an asymptomatic extrusion was reported. [32]

There are a number of studies that follow TVT patients for at least ten years. For example, Svenningsen et al. published their 10-year data on 483 women who had undergone TVT. They reported an objective cure rate of 90% and a subjective cure rate

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[28] FDA: Considerations about Surgical Mesh for SUI. www.fda.gov.
[29] ACOG/AUGS Practice Bulletin, Number 155, November 2015
[30] Ulmsten U, Falconer C, Johnson P, et al. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynocol J Pelvic Floor Dysfunction 1998;9:210-213
[31] Nillson CG, Kuuva N, Falconer C, et al. Long term results of the tension free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12(Suppl. 2), S5-8, Nillson CG, Palva K, Rezapour M, et al. Eleven years prospective follow-up of the tension free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19:1043-7
[32] Nilsson CG et al: Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary inctoninence. Int Urogynecol J, 2013; 1265-9

of 76%. Eighty-three percent of patients stated they were "very satisfied" and only 2.3% had undergone repeat incontinence surgery. *De novo* urgency incontinence was reported in 15% of patients available for 10-year follow up.[33]

Another ten-year follow-up study was published by Aigmueller et al. in 2011. Two hundred ten patients undergoing retropubic TVT were evaluated after 10 years. There was an objective clinical cure with negative clinical stress test in 84%. Subjectively, 57% considered themselves "cured" and 23% considered themselves "improved." Twenty percent of patients experienced *de novo* urgency.[34]

Also reported at the AUA meeting in 2014 was a long-term study from Korea of 206 patients who underwent TVT and were followed up to 13 years, with a mean of 162 months. The overall cure rate was 83% with a satisfaction rate of 68%. At 13-year follow up, one patient was found to have mesh exposure and two patients had *de novo* urgency.[35] These are just a few of the long term studies that have been published and which I address in more detail in my TVT General Report.

Given the high success rates and rapid recoveries, the retropubic midurethral sling became the new standard and replaced retropubic colpopsuspensions and the pubvaginal sling for the surgical treatment of stress urinary incontinence.[36] Furthermore, the retropubic TVT has been the most widely studied of any incontinence product currently available. As synthetic slings revolutionized the surgery for stress urinary incontinence, new sling kits using different synthetic materials and well as different surgical methods were introduced into the market. In 2001, Andonian et al. described the use of a top-to-bottom retropubic approach (SPARC, American Medical Systems, Inc) which proved to be equivalent to TVT in objective cure rate.[37] The SPARC, however, had a higher erosion rate than the TVT.[38] Other top-to-bottom retropubic approaches also entered the market.

In 2001, Delorme introduced the "outside-in" transobturator approach in order to avoid the passage of the needle into the retropubic space and subsequent potential injuries to the bladder and blood vessels.[39] This novel adaptation to an already proven technique provided the advantage of virtually eliminating the potential of bladder injury, large vessel injury and visceral injury. De Leval subsequently modified the transobturator procedure to the current "inside-out" technique in order to mitigate the risk of potential

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[33] Svenningsen R et al: Long term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J 2013; 1271-8.

[34] Aigmueller T et al: Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011;205(5): 496.

[35] Song et al: The long-term outcomes from TVT procedure for female stress urinary incontinence: data from minimal 13 years of follow-up. Abstract, AUA May 2014

[36] Dmochowski RR, et al: Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010; 183(5): 1906-14.

[37] Andonian S, Chen T, St-Denis B et al. Randomized clinical trial comparing suprapubic arch sling (SPARC) and tension-free vaginal tape (TVT): one-year results. Eur Urol 2005;47:537-41

[38] Lord HE, et al: A randomized controlled equivalence trial of short-term complications and efficacy of tension-free vaginal tape and suprapubic urethral support sling for treating stress incontinence. BJU Int. 2006; 98(2):367-76.

[39] Delorme E. Transobturator urethral suspension. Mini-invasive procedure in the treatment of stress urinary incontinence in women. Prog Urol 2003;44:724-30

vaginal or urethral injury, and potentially reduce the incidence of transient groin pain.[40][41] The transobturator sling had comparable efficacy to the retropubic midurethral sling and an improved safety profile, but with unique adverse events that included transient groin pain and obturator neurovascular injury.

TVT-O: Surgical Technique

The TVT-O is a minimally invasive procedure performed under sedation or general anesthesia. A small incision is made in the anterior vaginal wall at the level of the midurethra. Vaginal flaps are created on either side of the incision to allow for the passage of the sling. A tunnel from this incision to the inferior pubic ramus at the level of the mid-urethra is performed sharply and under digital guidance through the vaginal fornix. A protective metal guide is the inserted through this incision, just behind the inferior pubic ramus (under digital guidance through the vaginal fornix), perforating the obturator internus muscle. The sling, attached to a helical needle on either side, is passed through this incision over the protective guide, through the obturator internus muscle, through the muscles of the medical thigh, and out through a separate stab incision on the medical thigh. The procedure is done with digital guidance throughout the passage of the needles such that there is no "blind" passage. With specialized knowledge of pelvic and obturator anatomy, damage to the obturator neurovascular bundle is exceedingly unlikely as described by a number of cadaver studies.[42] [43] The sling is then positioned such that there is no tension on the sling. The needles are then cut, the plastic sheath is removed while maintaining tension-free positioning of the sling under the mid-urethra, and the sling is cut at the level of the skin. Though bladder injury is exceedingly rare with this procedure, cystoscopy can be performed to confirm the integrity of the bladder and urethral mucosa. All incisions are then closed and the procedure is complete. Experienced surgeons can perform this procedure in less than 15 minutes, with minimal blood loss and rare complications.

SAFETY AND EFFICACY OF TRANSOBTURATOR SLINGS: THE MEDICAL LITERATURE

Since its development, a large breadth of literature has become available, including high quality, long-term studies, randomized trials, and substantive meta-analyses, all supporting the safety and efficacy of TVT-O. This data, spanning continents and many years, has demonstrated consistent and reliable results regarding objective and subjective cures, as well as complication rates.

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[40] de Leval, J: Novel surgical technique for the treatment of female stress urinary incontinence: trnasobturator vaginal tape inside-out. European Urology 2003: 724-730.

[41] de Leval J, et al: The original versus a modified inside-out transobturator procedure: 1-year resuts of a prosective randomized trial. Int Urogynecol J 2010.

[42] Bonnet P, et al: Transobturator vaginal tape inside out for the surgical treatment of female stress urinary incontinence: anatomical considerations. J Urol 2005: 1223-8.

[43] de Leval et al: New surgical technique for treatment of stress urinary incontinence TVT-Obturator: new developments and results. Surg Technol Int. 2005: 212-21.

In 2010, Richter et al. performed a multicenter, randomized trial comparing 12-month outcomes with retropubic and transobturator slings on 597 women. In this study, published in the nation's arguably most selective medical journal, the New England Journal of Medicine, objective treatment success was achieved in 77.7% of the transobturator sling group (N=299). Postoperative voiding dysfunction requiring surgery occurred in 0% of patients in this group. Wound related adverse events occurred in only 3.3% of patients with serious adverse events of mesh/exposure/erosion in only 0.6% of patients in the transobturator group. There was no patient in the transobturator arm with a serious adverse event involving neurologic symptoms at the end of one year.[44] Two-year data on this study showed objective success rates were achieved in 72% of patients in the transobturator sling group with a patient satisfaction rate of 88%. De novo urge incontinence occurred in 0.3% and mesh exposure in 2.7% of the transobturator group.[45] The 5-year data on this study was published in the Journal of Urology.[46] Overall patient satisfaction after 5 years continued to be high at 85% in the transobturator sling arm. New mesh exposures/erosions were identified in 4 patients in the transobturator sling group.[47]

In 2015, Ford et al. published a systematic meta-analysis of midurethral slings for the Cochrane Library.[48] This analysis included 81 trials and 12,113 women who had undergone midurethral slings. Of these, 55 trials including 8652 women compared transobturator slings to retropubic slings, and over 80% of the studies analyzed in this review (66 out of 81 trials) involved TVT Retropubic or TVT-O. The goal of this updated meta-analysis was to provide information on the medium and long-term safety and efficacy of midurethral slings, including TVT-O As described by the authors, "we now have 18 years-worth of data since the initial report of retropubic mid-urethral tape, and it is over 11 years since the first randomised trials of tension-free vaginal tape and transobturator tapes were published."

Short term (up to one year) subjective cure in the transobturator group was similar to that in the retropubic group and ranged from 62% to 98%. In the long term (greater than 5 years), subjective cure rates in the transobturator group ranged from 43% to 92% and from 51% to 88% in the retropubic group. With regard to complications regarding slings, "the overall rate of adverse events remained low," though transobturator slings had a lower morbidity when compared to retropubic slings. While postoperative voiding dysfunction, transient suprapubic pain, bladder perforation, vascular/visceral injury, mean operating time, operative blood loss and length of hospital stay were lower with transobturator slings, overall rates of transient groin pain were higher in the transobturator group. The overall rates of erosion/extrusion/exposure were low in both groups, with a rate of 2.4% in the transobturator group.

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[44] Richter et al, Retropubic versus transobturator midurethral slings for stress urinary incontinence. N Engl J Med. 2010, 362 (22): 2066-76.

[45] Albo ME et al: Treatment success of retropubic and transobturator midurethral slings at 24 months. J Urol. 2012, 2281.

[46] Kenton K et al: 5-year longtitudinal followup after retropubic and transobturator midurethral slings. J Urol. 2015. 193(1):203-10.

[47] Hijaz A: Female Urology and Urodynamics at AUA 2014. AUA News. October 2014: 11-13.

[48] Ford AA, et al: Mid-urethral sling operations for stress urinary incontinence in women. The Cochrane Library. 2015, Issue 7.

When the authors looked at TVT-O ("obturator medial-to-lateral approach") versus other transobturator slings ("lateral-to-medial approach"), short- and medium-term (1-5 years) subjective cure rates were similar, as were duration of procedure, operative blood loss, length of hospital stay, de novo overactive bladder, vaginal erosions, groin pain, repeat incontinence surgeries and time to return of normal activities. However, vaginal perforation was less likely to occur in the non-TVT-O transobturator group than in the TVT-O group. Voiding dysfunction occurred more frequently in the TVT-O group, though the average rate across both groups was low at 5.5%. With regard to sexual function in the transobturator group, there was significant improvement in scores on validated questionnaires in both transobturator groups with no significant difference between the two groups. According to Ford, "rates of dyspareunia following surgery were extremely low, with evidence of resolution by 24 months."

Schimpf[49] et al. reported on a systematic review and meta-analysis of studies comparing a variety of anti-incontinence procedures with particular emphasis on mid-urethral slings. Though this analysis compared different slings to a variety of other approaches for the treatment of stress urinary incontinence, the authors assessed 17 trials of 995 women who underwent TVT-O. Follow up duration on these studies ranged from 12 months to 36 months. Overall, the authors found no significant difference in objective cure rates between midurethral slings and Burch colposuspension, though the metanalysis of subjective cure rates for favored midurethral slings over pubovaginal slings. There was no statistical difference between objective and subjective cure rates for obturator versus retropubic slings. Adverse events were variable between slings, with overactive bladder symptoms being more common after retropubic slings as opposed to transobturator slings. In the transobturator group, the complication rates were low: the rate of dyspareunia was 0.16% , return to OR for "erosion" was 2.7%, "exposure" was 2.2%, "wound infection" was 0.74%, UTI was 4.3%, bowel injury was 0%, nerve injury was 0.61%, overactive bladder was 5.3%, transient retention was 2.3%, retention greater than 6 weeks was 2.4%, return to OR for urinary retention was 1.1%, groin pain was 6.5%, leg pain was 16%, and vaginal perforation was 0.35%. The authors further noted that dyspareunia with slings was rare.

Tommaselli et al performed a systematic review looking at medium- and long-term outcomes after midurethral slings.[50] The review included 39 studies (11 RCT's and 38 non-randomized studies) covering 6406 women being followed for a minimum of 36 months for transobturator slings and 60 months for retropubic slings. Both retropubic and transobturator slings were found to have high subjective and objective cure rates in the long and medium term, with a very high safety profile for midurethral slings. The authors identified 12 studies involving 1,405 women who had undergone TVT-O with follow-up of 36 months or greater, including 4 studies with follow-up of 5 years or more. No significant differences in complication rates were seen between TVT-O and other transobturator slings, although vaginal perforation was less common in patients undergoing TVT-O. Vaginal "erosions" were identified in 2.7% of patients who had

[49] Schimpf MO et al: Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 210.

[50] Tommaselli GA, et al: Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J 2015.

undergone transobturator slings, and in 2.1% of patients after retropubic slings. Post-operative pain was identified in 6% of patients after transobturator slings. However, persistent pain beyond the post-operative period was reported by only 30 patients in the transobturator group (N=2,432) for a rate of 1.2%. Persistent voiding problems were seen in 30 (1.2%) patients in the transobturator group, without mention of preexisting voiding problems. The study demonstrates that both retropubic and transobturator midurethral slings are highly effective and have a low risk of complications. Furthermore, the analysis demonstrates, consistent with my experience and opinions, that complications, when they do infrequently occur, are "seldom severe."

Laurikanian et al randomized 267 patients to TVT or TVT-O, and the 5-year data on this high quality study were published in 2014.[51] [52] At the end of 5 years, 95% of women were assessed. The objective and subjective cure rates in the TVT-O group were 86.2% and 91.7%, respectively. Adverse events were low, with de novo incontinence experienced in only 2.4% of the TVT-O group. At the end of 5 years, only one patient (in the TVT-O group) had a "tape extrusion" at the midline, which occurred one year post-operatively. No other patient experienced any other tissue reaction, erosion or "tape protrusion." One patient (in the TVT-O group) required sling lysis for urinary retention with resolution of retention but persistence of urgency symptoms.

Zhang A. et al. recently reported on a randomized trial of 140 patients with stress urinary incontinence randomized to TVT or TVT-O with mean follow-up of 95 months.[53] The primary outcome was the "proportions of patients with long-term postoperative complications," with a secondary outcome of cure rate, quality of life and sexual function. There was no difference between the two groups with respect to long-term complications. The primary long-term complication was de novo voiding (15.8%) and storage symptoms (10.8%) in the TVT-O group. Five of the TVT-O patients (8.05%) experienced a tape exposure, though only one patient in the TVT-O group required sling revision. Groin/thigh pain occurred in 4 patients in the TVT-O group (6.45%). Though 5 patients in the TVT-O group experienced de novo dyspareunia, the PFIQ-7 scores remained improved even 8 years after both procedures, and no difference in PISQ-12 scores was observed after either TVT-O or TVT. The objective cure rate at the end of 95 months was 69.35% for the TVT-O group. The authors concluded that "most complications were not consequential, and the patients' QOL retained significant improvements in the long term."

Cheng et al. evaluated outcomes in 103 patients who underwent TVT-O with 5-year follow-up.[54] Objective cure was achieved in 92% at the end of 5 years. The most common complaint after surgery was groin pain, which was observed in 24.3% within the first 6 months of surgery. At one year post-operatively, only 3.8% of women complained

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[51] Laurikainen EH, et al: Retropubic compared to transobturator tape placement in treatment of urinary incontinence: a randomized controlled trial. Obstet Gynecol 2007; 109:4.

[52] Laurikainen E, et al: Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. European Urology 2014; 65: 1109-1114.

[53] Zhang Z, et al: Retropubic tension-free vaginal tape and inside-out transobturator tape: a long-term randomized trial. Int Urogynecol J. 2016: 103-11.

[54] Cheng D, et al: Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. European J Ob Gynecol and Reproductive Bio 2012; 228-231.

of groin pain. One patient was identified with "mesh erosion" and 3 patients required sling lysis for urinary retention.

Liapis et al. published their 4-year data on 74 women who had undergone TVT-O alone and 41 patients who had undergone TVT-O with anterior repair.[55] At 4-year follow-up, objective cure rates based on pad test findings were 82.4% and 80.5% with improvement rates of 6.8% and 7.4%, respectively. The incidence of de novo urge incontinence was 8.1% in the TVT-O only group and 9.7% in the TVT-O/anterior repair group. Post-operative urgency was identified in 10.8% of the TVT-O only group and 12.1% in the TVT-O/anterior repair group. There was one patient in the study (TVT-O only group) who required sling lysis for urinary retention with restoration of normal voiding and post-lysis continence. The incidence of post-operative UTI was 8.1% for the TVT-O only group and 7.3% for the TVT-O/anterior repair group. Asymptomatic mesh exposure was identified in one patient in the TVT-O only group and in one patient in the TVT/anterior repair group, for an exposure rate of 1.7%. Both cases were identified within 5 months of surgery by the patients' sexual partners, and both were managed by simple excision of exposed mesh.

Athanasiou et al. reported on their study of 144 consecutive women who underwent TVT-O with median follow-up of 90 months.[56] Objective and subjective cure rates were 81.5% and 83.5%, respectively. They found that advancing age and concomitant vaginal hysterectomy were associated with a higher risk of subjective failure, as did more severe pre-operative apical prolapse. De novo urgency occurred in 7%. Sling lysis was required in one patient (0.8%) for retention, and partial sling excision was required for one patient (0.8%) for a midline vaginal exposure that was identified one year post-operatively. No patient reported persistent groin pain at long-term follow-up.

Serati et al. reported on a 5-year study of 191 women undergoing TVT-O.[57] Objective and subjective cure rates were 90.3% and 90.8% , respectively, at the end of 5-years. De novo overactive bladder symptoms was reported by 24.3% of women at 1-year follow-up and in 19.5% at 5-year follow up. Sling revision was required in one patient for voiding dysfunction. Two patients were identified as having vaginal exposures at 1 year, one who underwent sling removal. Transient groin pain (24 hours after surgery) was reported in 9.9% of patients, and 3.1% of patients reported groin pain one month post-operatively. At 1 year post-operatively, groin pain persisted in 1% of patients. At 5-year follow-up, there was no reported patient with groin pain remaining.

Waltregny et al. reported on 102 women who had undergone TVT-O with minimum 3-year follow-up.[58] Surgical cure at 3 months was achieved in 88% and improvement in stress urinary incontinence was achieved in 9.3%. These rates were

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[55] Liapis A, et al: Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. European J Ob Gyn and Repr Bio 2010:199-201.

[56] Athanasiou S et al: Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: Why do tapes fail? Int Urogynecol J 2014: 219-225

[57] Serati et al: TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up. European Urology 2013:872-878.

[58] Watregny D, et al: TVT-O for the treatment of female stress urinary incontinence: results of a prospective study after a 3-year minimum follow-up. European Urology 2007.

similar to those reported by the authors at 1 year. Throughout the duration of the study, no "erosion," neurologic complication or persistent pain was noted. Four patients required sling lysis for urinary retention. De novo overactive bladder symptoms were reported by 11% of patients. Of patients with pre-operative overactive bladder symptoms, 70-75% experienced disappearance of or improvement in these symptoms postoperatively. Only one patient reported having recurrent urinary tract infections, though this patient had undergone pelvic radiation for rectal cancer.

Palva et al reported on 267 women randomized to TVT or TVT-O with 36-month follow-up.[59] At final follow-up, objective cure rate was 89.5% in the TVT-O group, with 95.2% of women who would "recommend the operation to a friend." De novo urgency was reported in 5.6% of the patients in the TVT-O group. Five patients in the TVT-O group required long-term antibiotics for recurrent UTI. One patient in the TVT-O group underwent sling resection due to vaginal exposure at 1-year follow-up. No other vaginal wall or other erosions were reported at the 3-year visit. One patient in the TVT-O group required sling division for urinary retention. When compared to TVT, there was no significant difference in cure rates and complication rates.

TVT-O has excellent efficacy and durability. Its therapeutic benefits and safety profile far outweigh the risks as a surgical treatment option for female SUI. The data support this opinion and further support that the mesh used in the TVT-O is appropriate, safe and effective.

MATERIAL PROPERTIES OF TVT-O MESH

The mesh used in the TVT-O implant is made of PROLENE®, which is Ethicon's nonabsorbable polypropylene mesh. This monofilament mesh is knitted with large pore size, and as such integrates well into surrounding tissue. PROLENE® is safe and clinically appropriate for transvaginal use to treat stress urinary incontinence, as evidenced by the robust body of literature detailing its safety and efficacy. The same mesh has also had applications in general surgery for hernia repair. Furthermore, polypropylene suture has been in wide surgical use for decades, including use in wound closures for abdominal and flank surgeries.

After the placement of polypropylene mesh, one would expect a tissue reaction to occur. Such tissue reactions may occur with the placement of any foreign body, such as suture, into human issue. Human tissue scars after surgery, which is not only the result of surgery itself, but also as the result of the placement of any foreign body, prosthesis or implant. This tissue reaction, in the case of PROLENE®, is very likely to be one of the reasons why TVT-O is so effective.

In clinical use, this inflammatory process has little to no clinical relevance. As a surgeon who has seen this tissue reaction in weeks to months to years after placement for

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[59] Palva K et al: A randomized trial comparing tension-free vaginal tape with tension-free vaginal tape-obturator: 36-month results. Int Urogynecol J 2010: 1049-1055.

a variety of reasons, not necessarily pathologic, I can attest to the fact that this reactive tissue response is predictable and consistent from patient to patient, and very likely occurs in every patient after the placement of the sling. If the PROLENE® mesh used in TVT and TVT-O had the dangerous properties postulated by its adversaries, it would likely cause many more negative clinical consequences than what has been described in the medical literature over the last 20 years of use. To the contrary, in clinical use, the mesh used in these slings is effective with extremely low complication rates and minimal morbidity, as is evidenced by the large body of literature supporting this. Therefore, despite reports of in vitro "cytotoxicity," there is no such evidence of clinical, in vivo "cytotoxicity" in the medical literature.

Furthermore, infection of the mesh or local surgical site infection is an extremely rare complication with respect to midurethral slings as documented in all short and long-term studies reviewed in this report. Furthermore, in my personal experience of approximately 1,000 mesh slings, not one of my patients has experienced this complication.

TVT has been offered in mechanically cut mesh since its inception and in laser cut mesh since 2006, enabling surgeons a choice in this property of the mesh. Though some surgeons prefer mechanically cut mesh and some prefer laser cut mesh, there is no data in the medical literature to support one type of cut over the other. Similarly, though some surgeons may feel that the mechanically cut mesh results in mesh fraying and loose particles, in my experience this fraying is clinically inconsequential and not responsible for any untoward outcome of surgery. Similarly, there is no data in the medical literature to support this claim.

There is no data in the medical literature supporting the notion that the PROLENE® mesh used in the TVT family of products is not biocompatible, cytotoxic, or creates an inappropriate inflammatory or chronic foreign body response that has any adverse clinical impact. Similarly, there is no data to support that the pore size is insufficient or creates any adverse clinical reactions or consequences whatsoever. The data also does not support claims that the mesh used in TVT degrades in any way that is clinically significant, or that mechanical cut mesh is inferior in any way to laser cut mesh, or vice versa. Indeed, neither the literature nor my extensive clinical experience shows any clinical difference between the two types of mesh. The data does not support claims that the mesh, regardless of which type, is stretched during proper clinical use and implantation such that it causes or contributes to any adverse clinical impact. The data does not support that there is particle loss with mechanical cut mesh or, if there is some loss, that it has any clinical impact at all. The data does not support that the mesh implant ropes or curls unless too much tension is placed on the sling during implant. The data also does not support claims that the mesh causes or contributes to cancer.

Finally, there is no evidence in the medical literature to suggest that there exists any other design of sling that would eliminate or even reduce the potential risks of the mesh used in TVT-O. This includes Gynemesh PS, Ultrapro (the material used in Prolift +M and Artisyn) or the laser cut version of TVT's PROLENE® mesh. Gynemesh PS

and UltraPro have not been studied widely in an SUI indication, and certainly not to the extent of TVT's and TVT-O's PROLENE® mesh. Therefore, it is not possible to conclude with any level of certainty or probability that they would reduce or eliminate the potential risks of TVT-O.

For example, Okulu et al. studied the use of Vypro, UltraPro and Gynemesh PS/Prolene Soft Mesh in groups of only 48 patients each. This study, however, utilized this mesh with a novel surgical technique. The slings were wide-based, rather than a tape, they were employed through an inverted "A"- shaped incision, and they were fixed and tensioned, rather tension-free as TVT/TVT-O is. It is not at all a comparison to TVT/TVT-O given the significant variation in technique. Furthermore, although the authors describe it as a randomized control trial, there was no control group that utilized the TVT PROLENE mesh. The results did not indicate reduction – much less elimination – of risks such as vaginal exposure: the study noted rates of 4.25% and 2.08% for Prolene Soft and Ultrapro, respectively, a difference of only one patient. In Table 6 of Novara's 2008 meta-analysis, several studies of TVT are listed (with 24 month follow up) demonstrating vaginal exposure rates between 1-2%. In any event, the patient groups in this single study by Okulu et al. are far too small to draw any meaningful conclusion that these materials reduce the risks of PROLENE®. Moreover, Ethicon tested a partially absorbable mesh for potential use in TVT and experienced problems in benchtop and cadaveric testing with respect to sheath removal from and sterilization of the partially absorbable mesh. (ETH.MESH.09922570-78.) Finally, Gynemesh PS and Ultrapro, when used to treat prolapse, present similar risks (albeit at higher rates because of the prolapse indication), reflecting the fact that risks exist whenever an implantable material is used.

POTENTIAL COMPLICATIONS

As with any anti-incontinence surgery, TVT-O carries the risk of urinary retention, overactive bladder (either *de novo* overactive bladder or persistence of pre-existing overactive bladder), blood loss, hematoma, urinary tract infections, bowel injury, vascular injury, bladder perforation, urethral perforation, vaginal perforation, dyspareunia, post-operative pain and DVT. A meta-analysis by Novara looking at complications after anti-incontinence surgeries showed that complication rates were similar after TVT and Burch colposuspension with respect to the parameters listed above. The rate of bladder perforation was more common after TVT, and reoperation rates were significantly higher after Burch colposuspension.[60]

Urinary Retention

Retention, which is the patient's inability to void, is a known possible complication of all anti-incontinence procedures, and retention after the placement of

[60] Novara G et al: Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur Uro 2007; 288-309.

TVT and TVT-O are no exception. All patients prior to any anti-incontinence procedure should be counseled regarding the possibility of urinary retention and the potential for sling revision should this occur.

Nonetheless, urinary retention is a complication that can be minimized when using TVT by proper tension of the sling. As per the TVT-O IFU, "place a blunt instrument…between the urethra and the tape during removal of the plastic sheaths, or use other suitable means during sheath removal to avoid positioning the tape with tension." Furthermore, the IFU warns that "too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction."

In the Schimpf meta-analysis which includes studies comparing the Burch procedure to midurethral slings, retention lasting less than 6 weeks in the transobturator midurethral sling group occurred in only 2.3% of cases and in 17% of Burch cases. Retention lasting more than 6 weeks occurred in only 2.4% of patients in the transobturator midurethral sling group, as compared to 7.6% of patients in the Burch group. The incidence of return to the operating room for retention in the transobturator group was 1.1% as opposed to 3% in the pubovaginal sling group.[61] Similarly, in the TOMUS trial, the rate of voiding dysfunction requiring a surgery and/or catheter use in the trans-obturator group was 0%.[62]

In the case of TVT-O, urinary retention, should it occur despite proper tensioning, is an easily correctible situation. Patients present with retention immediately post-operatively. If a patient has been unable to void in the 7 to 14 day postoperative period, the incision can be opened under local anesthesia or sedation and the sling can be loosened. After the two-week postoperative period, tissue integration may prevent the easy loosening of the sling and the sling may need to be incised to correct urinary retention. As such, it is my personal preference to simply loosen the sling within the two-week post-operative period in the unusual event that a patient is in urinary retention after a sling.

Overactive Bladder

It is well known that any surgical procedure for the treatment of stress urinary incontinence comes with a potential risk of *de novo* urge incontinence and/or overactive bladder. Furthermore, it is well known by clinicians that midurethral slings are not designed or indicated to treat overactive bladder symptoms. Nonetheless, rates of *de novo* overactive bladder symptoms are low in patients undergoing transobturator sling procedures. In the TOMUS trial, *de novo* urge incontinence occurred in 0.2% of patients in the transobturator sling group at 2 years.[63] Persistent urge incontinence, however, was reported in 12.7% of patients undergoing transobturator midurethral sling. In the

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[61] Schimpf MO et al: Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 210.

[62] Brubaker L et al: Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the trial of midurethral slings (TOMUS) study. Am J Obstet Gynecol 2011; 205.

[63] Albo ME, et al: Treatment success of retropubic and transobturator midurethral slings at 24 months. J Urol 2012; 188: 2281-2287.

Schimpf meta-analysis, the incidence of overactive bladder was 5.3% in the transobturator sling group in comparison to 8.6% in the pubovaginal sling group and 4.3% in the Burch group.[64]

Albo et al. performed a multi-center, randomized trial comparing outcomes in women undergoing autologous rectal fascial pubovaginal slings and Burch colpopsuspensions.[65] Postoperative treatment for urge incontinence was required in 27% of patients in the Burch group and 20% of patients in the autologous fascial sling group. Furthermore, in the AUA Guildelines meta-analysis for the surgical management of stress urinary incontinence, *de novo* urge incontinence occurred in a median of 8% of patients undergoing the Burch procedure, 9% of patients undergoing autologous fascial slings without bone anchors, 28% of patients undergoing cadaveric slings with bone anchors, and 6% of patients undergoing synthetic midurethral slings at 12 to 23 months postoperatively.[66]

Interestingly, a study presented at the AUA Annual Meeting 2014 (PD33-03) found that 60 to 70% of women with mixed urinary incontinence undergoing midurethral sling surgery experienced improvement in their overactive bladder symptoms at 12 months. This initial improvement however diminished with time.[67] Other studies have shown similar outcomes.[68]

In counseling patients with mixed urinary incontinence for surgical treatment, it is critical to set the expectation that pre-existing overactive bladder symptoms may persist after surgery. Furthermore, the difference between overactive bladder and stress incontinence must be clearly explained to the patient since, in my experience, many patients do not understand the difference. It must be stressed to these patients that there are many treatments for overactive bladder that can be instituted should their overactive bladder symptoms persist after surgery. In fact, some patients may benefit from getting control of their overactive bladder symptoms prior to surgical intervention for their stress urinary incontinence.

Urinary Tract Infections

Urinary tract infections (UTIs) are common in women and often result in significant individual and societal burden.[69] Symptoms of a urinary tract infection include painful urination, pelvic pain, frequent and urgent urination, worsening urinary incontinence, and hematuria.

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[64] Schimpf MO et al: Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 210.

[65] Albo ME et al: Burch colpopsuspension versus fascial sling to reduce urinary stress incontinence. NEJM 2007; 356(21): 2143-2155.

[66] Appell RA, et al: Guideline for the surgical management of female stress urinary incontinence: update (2009).

[67] Hijaz A: Female Urology and Urodynamics at AUA 2014. AUA News. October 2014: 11-13.

[68] Watregny D, et al: TVT-O for the treatment of female stress urinary incontinence: results of a prospective study after a 3-year minimum follow-up. European Urology 2007.

[69] Foxman B: Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002; 11 (Suppl 1A): 5S-13S.

UTI's are common after any anti-incontinence procedure.[70] [71] Nygaard et al. reported on 1,252 women randomized to two different surgical trials with patients undergoing Burch procedures and midurethral slings (retropubic and transobturator) with or without concomitant prolapse surgery. They found that post-operative UTIs within the first 6 weeks after surgery were common (7-24%) and that pre-operative recurrent UTI was the only consistent risk factor associated with an increased risk of post-operative UTI. They also found that age was a risk factor for persistence of recurrent UTI after surgery.[72]

Like all anti-incontinence procedures, retropubic and transobturator slings are not immune to the risk of UTI. In the TOMUS trial, the incidence of culture proven UTI in the retropubic group was 1%, but in transobturator group was 0%.[73] Schimpf et al. reported in their meta-analysis an incidence of 11% in the retropubic sling group and 4.3% in the transbturator group, while they reported recurrent UTI in 5.9% of the Burch group and 4.2% of the pubovaginal sling group.[74] These numbers are consistent with the incidence of UTI amongst all patients undergoing anti-incontinence procedures.[75] [76]

Managing the occasional UTI with a simple course of antibiotics is usually the only treatments these patients need. In patients with recurrent urinary tract infections (greater than 4 UTI's per year) in the absence of any pathological source, consideration can be given to topical estrogen cream or suppositories in patients with vaginal atrophy and low dose antibiotic suppression. Patients with a known history of recurrent UTIs should be counseled preoperatively that their UTIs may persist after surgery.

Groin Pain/Leg Pain

Post-operative groin and leg pain following transobturator slings is a potential side effect that is seen more often with transobturator procedures. In my experience, and in that of Dr. De Lorme's as well as the experience of the medical literature listed above, most often this discomfort is temporary, with resolution within 48 hours, much less commonly persisting beyond a few days. Prior to surgery, it is important to warn the patient of the potential discomfort that is easily managed with over the counter analgesics.

Theories explaining the groin and/or leg pain that can follow the placement of transobturator slings include hyperflexion of the thighs that is required for positioning as well as blood contact with the obturator nerve. Furthermore, one does in fact expect

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[70] Albo ME, et al: Burch colpopsuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med 2007 (356): 2143-2155.
[71] Anger JT, et al: Complication of sling surgery among female Medicare beneficiaries. Obstet Gynecol 2007(109): 707-714.
[72] Nygaard I, et al: Risk factors for urinary tract infection following incontinence surgery. Int Urogynecol J. 2011(22): 1255-1265.
[73] Brubaker L et al: Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the trial of midurethral slings (TOMUS) study. Am J Obstet Gynecol 2011; 205.
[74] Schimpf MO et al: Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 210.
[75] Albo ME, et al: Burch colpopsuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med 2007 (356): 2143-2155.
[76] Anger JT, et al: Complication of sling surgery among female Medicare beneficiaries. Obstet Gynecol 2007(109): 707-714.

post-operative pain at the site of any surgery, and in this case the site of surgery is the groin.

Canel et al. retrospectively looked at patients undergoing TVT-O (N=50) versus patients undergoing TVT Abbrevo (N=50), a modified technique of TVT-O whereby the sling is shortened to 12 cm to avoid passage of mesh through the groin.[77] With a mean follow-up of 12 months, the authors found that although less postoperative pain was observed in the TVT-Abbrevo group, at 6 weeks after surgery there was no significant difference in pain between the two groups. All other complication rates were similar, as were the success rates.

The rates of post-operative pain after TVT-O could also perhaps be surgeon dependent. Serati et al published a prospective observational study of 372 procedures (all TVT-O) performed by a single surgeon.[78] The authors looked at trends regarding efficacy and adverse events relative to the number of procedures performed. Although they found that high objective and subjective cure rates with low complication rates could be achieved even at the beginning of a surgeon's learning curve, they also found that postoperative pain levels decreased with the increase in surgical expertise.

Wound Complications and Erosion/Exposure/Extrusion

Though rather infrequent, complications such as erosion, extrusion and exposure of mesh are the only clinical complications unique to the midurethral sling. In 2010, the International Urogynecological Association and the Interational Continence Society together published standard classifications of these terms. They defined "exposure" as the visualization of the mesh through the separated vaginal epithelium, "extrusion" as the gradual passing of the mesh outside of the body's tissues, and "erosion" as the entry or perforation of the mesh into an organ/viscus.[79]

The rates of these complications may vary according to sling composition as well as surgical technique and surgeon experience. For example, an experienced surgeon who performs a full thickness vaginal dissection is very likely to have a lower rate of exposure than the surgeon who performs a split thickness incision.

Furthermore, whenever a foreign body is implanted into the human body, one expects to see a foreign body reaction and inflammatory response upon histopathologic analysis, and mesh is no exception. That host reaction is not an adverse reaction. Rather, it is part of the normal process of healing. I am not a pathologist, but based upon my extensive experience as a clinician treating patients with approximately 1000 mesh slings, including managing their post-operative course, and based upon my review of the

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[77] Canel V, et al: Postoperative groin pain and success rates following transobturator midurethral sling placement: TVT ABBREVO system vesus TVT obturator system. Int Urogynecol J 2015, 1509-16.

[78] Serati M, et al: Is there a learning curve for the TVT-O procedure? A prospective single-surgeon study of 372 consecutive cases. Eur J Obstet Gynecol Reprod Biol 2015, 85-90.

[79] Zambon, J, Badlani, G., Algorithm for Management of Vaginal Mesh Exposure, AUA NEWS VOL 21 issue 1 January 2016 Page 3.

medical literature, this foreign body reaction does not typically translate into negative clinical outcomes for patients.

Vaginal exposure of mesh and mesh erosion are indeed an uncommon but real complication associated with the usage of transvaginal mesh. Though mesh exposure is usually asymptomatic in women, it can be problematic to male partners in sexually active women and may require topical estrogen cream or minor surgical intervention. Mesh erosion into other organs, however, is a more serious complication whereby the mesh can be found in the urethra or bladder. Such erosion can often cause worsening lower urinary tract symptoms, stone formation, and urinary tract infections and usually requires more complex surgical intervention. The etiology of erosion and exposures is unclear. Certainly, it is possible that the risk of exposure is higher in patients undergoing split-thickness dissection of the vaginal wall. It is also likely that a missed bladder perforation at the time of mesh insertion is the source of bladder erosion.[80]

Despite the uniqueness of these mesh complications, such complication in midurethral slings is uncommon. Of the 271 patients having undergone retropubic slings in the TOMUS trial, only 1 patient developed mesh erosion (0.3%) with an overall exposure rate of 2%, with most patients requiring no further surgical intervention.[81] No patient developed surgical site infection. The recently published longitudinal study on this trial looked at 291 of the original 298 women 5 years after sling surgery. There were 3 new mesh exposures occurring in years 3 to 5 (1%) and no new mesh erosions or wound infections in the retropubic sling group.[82]

In the Schimpf meta-analysis of transobturator slings, 2.7% returned to the operating room for "erosion" and 2.2% developed mesh exposure and the incidence of wound infection was 0.74%.[83] These numbers are consistent with other repeatedly low rates of sling exposure and erosion.

It should also be made clear that iatrogenic mesh exposures can occur should a vaginal perforation go unidentified during placement of the procedure. It is critical to assess the vaginal fornices for vaginal perforation during the procedure in order to prevent an iatrogenic exposure.

Claims of Mesh "Migration" and Contraction

Based on my vast experience with placing transvaginal mesh and my review of the relevant medical literature, polypropylene slings do not "migrate" or move in a clinically significant way in the postoperative setting if the surgeon has performed the dissection properly. The IFU states that a 1 cm incision should be made sagitally on the

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80 But I, et al: Prolene tape in the bladder wall after TVT procedure—intramural tape placement or secondary tape migration?" Int. Urogynecol. J 2005; 16:75076.

81 Brubaker L, et al: Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Miduretral Slings (TOMUS) study. Am Obst Gyn 2011; 205: 498.

82 Kenton K, et al: 5-Year longitudinal followup after retropubic and transobturator mid urethral slings. J. Urol. 2015; 193: 201-210.

83 Schimpf MO et al: Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; 210.

anterior vaginal wall 1 cm proximal from the urethral meatus. Limiting the incision and dissection to this standard enables the proper positioning of the sling at the level of the midurethra. However, a large incision and a more extensive dissection may allow the sling to slip proximally at the time of placement to the level of the bladder neck, where it is not intended to be.

Provided, however, that the incision is performed consistently with the IFU, there is no room for the tape to migrate. Upon exploration merely days after sling placement, significant force is required to adjust sling position and/or tension. In fact, sling adjustments can rarely be performed without lysis after 14 days of placement. This is likely due to tissue in-growth that rapidly occurs soon after sling placement, making it a challenge for the sling to move, whether by force or so-called "migration."

This opinion is supported by case reports of patients who developed urinary retention after sling placement and concomitant anterior repairs through a single large incision.[84] Of 130 cases of patients undergoing TVT, 31 patients had concomitant anterior repairs. Of these 31 patients, 28 patients had slings placed through a separate incision and 3 patients underwent a sling and anterior repair through one single large incision. Of those 3 patients, 2 patients developed urinary retention and were found to have their slings at the bladder neck on reoperation. It should be noted that of their 130 patients, only 3 developed urinary retention necessitating surgical intervention and 2 of those 3 patients had their slings placed through this large incision. It was the conclusion of these authors, rightfully so, that the TVT midurethral sling should be placed through a small, separate incision to ensure proper placement at the midurethra as per the IFU.

Furthermore, Dietz et al. looked at TVT sling position longitudinally over a median of 1.6 years by ultrasound.[85] They found no evidence for contraction or shortening of the TVT. Furthermore, slow and gradual caudal descent of the sling occurred along with the surrounding tissues and structures. This suggests appropriate integration of the TVT into surrounding tissues, which naturally descend over time. Additionally, tape mobility on Valsalva remained unchanged, suggesting that stiffening of the tape or surrounding tissues does not occur over time. Thus, this study supports the notion that TVT does not contract, shorten or "migrate" in any clinically significant way.

Pelvic Pain

Persistent pelvic pain lasting beyond the post-operative recovery period is a rare outcome of transobturator slings. In the TOMUS trial, only 2% of patients having undergone transobturator sling alone developed persistent self-reported pain.[86]

Although this outcome is clearly rare, some patients undergoing TVT-O may develop new onset pelvic pain that persists after the postoperative period. The etiology

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[84] LaScala et al: Incomplete bladder emptying after the tension-free vaginal tape procedure, necessitating release of the mesh: a report of three cases. J Reprod Med 2003. 48(5): 387-90.

[85] Dietz HP et al: Does the tension-free vaginal tape stay where you put it? Am J Obstet Gynecol 2003. 188(4): 950-953.

[86] Brubaker L et al: Adverse events over two years after retropubic or transobturatoe midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study. Am J Obstet and Gynecol 2011, 205: 498.

of this is unclear, though some studies suggest that inappropriate placement of the sling may be responsible for this unusual complication. Rigaud et al published a study of 32 patients undergoing removal of midurethral slings for chronic pelvic pain.[87] Of the 32 patients, 17 patients had undergone retropubic TVT and 15 patients had undergone transobturator slings. Surgical exploration of these patients revealed "abnormal tape position" or "excessive tape traction." All of these positions clearly reflect incorrect placement, likely the result of surgical technique that deviated from the TVT IFU.

Dyspareunia

Dyspareunia is variably reported as a complication of midurethral sling surgery and is a risk of any pelvic floor surgery. However, few of the larger and long-term studies demonstrate an appreciable incidence of dyspareunia resulting from TVT-O. In both the Schimpf and Ford meta-analyses, the incidence of dyspareunia after transobturator slings, and midurethral slings in general, is exceedingly low. This is confirmed in many of the long-term studies included in this report.

Zyczynski et al. prospectively assessed the effects of midurethral sling surgery on sexual function in patients enrolled in the TOMUS trial. Mean sexual function scores improved significantly in both the transobturator sling group and the retropubic group, with no significant difference between the two. Furthermore, dyspareunia, coital incontinence, and fear of coital incontinence improved significantly after sling surgery.[88] Naumann et al. reported on 75 women who underwent the TVT procedure. Postoperative sexual function questionnaire scores (FSFI) improved from 24.6 to 28.5, which may be explained by the efficacy of the treatment (88% total continence rate).[89]

In addition to the infrequent incidence of dyspareunia in the medical literature, as discussed above, it is clear from my personal experience in treating a large volume of women with incontinence that dyspareunia after sling surgery (in the absence of concomitant pelvic floor reconstruction) is a rare outcome. Rather, sexual function usually improves. In a patient with stress incontinence, sexual activity is either avoided or less enjoyable due to fear of coital and/or orgasmic incontinence. Cure of their stress incontinence and likewise coital/orgasmic incontinence almost invariably results in improved sexual desire, more frequent sexual activity and more fulfilling intimacy.

Claims that Slings Cause Malignancy

Though some pontificate that there is an association between midurethral slings and malignancy, there is no data in the medical literature to support such claims. King et al. retrospectively reviewed 2361 patients who underwent polypropylene sling placement. Mean follow-up was 42 months, with follow-up extending up to 122 months. The rate of

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[87] Rigaud J et al: Functional results after tape removal for chronic pelvic pain following tension-free vaginal tape or transobturator tape. J Urol 2010, 184(2): 610-615.

[88] Zyczynski HM, et al: Sexual activity and funstion in women more than 2 years after midurethral sling placement. Am J Obstst Gynecol. 2012; 207(5): 421.

[89] Naumann et al: Sexual function and quality of life following retropubic TVT and single-incision sling in women with stress urinary incontinence: results of a prospective study. Arch Gynecol 2013; 959-966.

bladder cancer was 1 of 2361 (0.0%) with the same rate of vaginal cancer. This level of incidence cannot be attributed to the mesh over other patient factors. No sarcomas were described.[90]

Claims of Mesh Degradation and "Subclinical Infection"

There is no medical literature supporting the notion that polypropylene mesh "degrades" in any clinically significant way. Polypropylene by design is intended to be clinically present and supportive in its function. This is readily apparent to surgeons upon re-operation, if necessary. The mesh is found intact without clinical evidence of biodegradation. This is in comparison to biologic grafts, which on reoperation can often be invisible, degraded and non-supportive.[91] Given the large body of literature on the long-term efficacy of polypropylene slings with over 17 years of follow-up, it stands to reason that the polypropylene in slings, does not degrade in any substantial or clinically significant way.[92]

Clave et al examined explanted mesh implants from women with mesh erosion and/or "infection" after mesh-augmented reconstructions and compared them to a control group of pristine implants that had not been implanted. Using histological analysis, electron microscopy, and chemical analysis, electron microscopy, the authors concluded that oxidation of polypropylene "can neither be confirmed nor excluded" in the in vivo environment. Furthermore, the study compared mesh explanted from patients with complications to pristine, pre-implanted mesh, rather than mesh explanted from patients without complications. The authors therefore concluded that "prediction of normal in vivo sling material aging or the range of consequences in the clinical state beyond the observed samples is not possible. Due to small effective sample size, it is not possible to categorically conclude on the basis of statistical analysis even if a clear tendency is present." This study, therefore, by no means supports the notion that degradation, as seen under an electron microscope, has any clinical impact on the performance of polypropylene mesh in vivo.[93]

Similarly, there is no data in the medical literature supporting an in vivo, clinically significant "infection" related to polypropylene mesh. The tissue reaction that occurs after mesh placement is considered to be a normal physiologic reaction to a foreign body that occurs with all materials, including but not limited to sutures, grafts, surgical implants and metallic devices.

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[90] King AB, et al: Is there an association between polypropylene midurethral slings and malignancy? Urology 2014;789-92.

[91] Woodruff AJ et al: Histological comparison of pubovaginal sling graft materials: a comparative study. Urology 2008: 85-89.

[92] Nilsson CG et al: Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013: 1265-9.

[93] Clave A et al: Polpropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010: 261-270.

Wang et al reported on a prospective "case-controlled study" comparing microbiological and immune-histochemical analyses of excised vaginal and peri-urethral tissue from 24 women with de novo urge symptoms after mid-urethral sling with TVT, Sparc or Monarc.[94] The authors performed urodynamics on each post-operative patient at the 6 month visit or when then complained of "urge sensation." "De novo urge symptoms" was defined as "any elevation of the detrusor pressure with urge sensation or urge incontinence during a filling cystometry, performed postoperatively." The authors enrolled 68 women as the "urgency" group. All patients were initially treated conservatively. Excision of the sling and peri-urethral tissue was performed for those patients whose symptoms persisted despite conservative measures. The control group consisted of 12 women who had undergone midurethral sling but who developed symptomatic prolapse without de novo urgency symptoms 6 months after their sling surgery. These women underwent excision of peri-urethral tissue composed of vaginal wall, peri-urethral fascia and "possible urethral muscles" near the sling at the time of their prolapse surgery. The authors found higher levels of immune activity and gram-positive bacteria in the study group.

This study in no way provides evidence that any kind of "subclinical infection" or bacterial/immunogenic mechanism is responsible for de novo urgency after mid-urethral sling surgery. First, the sample size is quite low, with only 12 "control" subjects. Furthermore, the control subjects are not truly controls, as their specimen did not include a portion of the sling and the tissues incorporated in the sling, whereas the study specimens did include those tissues and the sling itself. Additionally, the study is severely flawed by the fact that the patients routinely underwent UDS at 6 months post-operatively regardless of their symptomatic complaints, and they were considered to be surgical candidates for mesh excision by virtue of their urodynamics findings. Finally, de novo urgency is not a complication of sling surgery that is exclusive to midurethral slings. The rate of de novo urgency after mid-urethral slings is consistent with the rate of de novo urgency after non-mesh anti-incontinence procedures. If there was some mechanism exclusive to slings, such as this supposed "subclinical infection" causing de novo urgency, we would more globally see a significantly higher rate of de novo urgency in mesh slings versus other anti-incontinence procedures—and we do not. Similarly, the chronic inflammation seen on the slides of the asymptomatic controls debunks the theory that this physiological reaction results in adverse outcomes. For these reasons, this study's conclusions linking de novo urgency after mesh slings to "subclinical infection" is invalid, and in no way suggests that the mesh used in TVT-O causes this same "subclinical infection."

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94 Wang AC et al: A microbiological and immunohistochemical analysis of periurethral and vaginal tissue in women with de novo urge symptoms after mid-urethral sling procedures—a prospective case-controlled study. Int Urogynecol J Pelvic Floor Dysfunct. 2008: 1145-50.

SUMMARY OF OPINIONS:

For the reasons set forth above, it is my opinion to a reasonable degree of medical probability that:

1. The Gynecare TVT-O is a safe and effective product that is supported by a substantial body of clinical data over the past 20 years. Midurethral slings, including transobturator slings, are now considered the "gold standard" for the management of stress urinary incontinence. It is a suitable (if not the best) treatment option for many women who suffer from this condition. Based on my experience of approximately 1000 mesh slings, my review of the medical literature, and my training, it is my opinion that TVT-O is not defectively designed.

2. The mesh used in the TVT-O implant is a safe and effective material for use in this indication – regardless of whether it is mechanically cut or laser cut. Polypropylene mesh and sutures have been used for decades. As a clinician with extensive experience in implanting mesh slings and managing the post-operative course of patients, it is my opinion that pore size of the mesh tape in TVT-O is large enough to allow for proper tissue ingrowth. There is no evidence to suggest that the manner in which TVT mesh is cut has a clinical impact upon patients.

3. A foreign body/inflammatory response is an expected and physiological outcome of the placement of any surgical implant. There is nothing in the medical literature to support that this response has any negative impact on clinical outcomes when the TVT-O is placed correctly.

4. The extensive clinical data on TVT-O does not demonstrate that the TVT-O mesh implant degrades in the body in any manner that has a clinical impact on patients. If it did, surgeons, including myself, would see far lower long-term efficacy in their repairs.

5. The medical literature does not support the notion that the mesh implant in TVT-O migrates if it is implanted in accordance with the procedure set forth in the IFU.

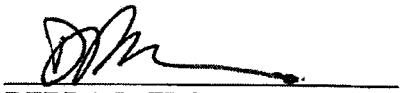
6. The medical literature does not demonstrate complications associated with excessive contraction of the tissues surrounding the mesh. Nor does it demonstrate that the mesh ropes or curls in the absence of overtensioning during implant.

7. The possible risks of TVT-O are appropriately described in the TVT IFU and in Ethicon's professional education materials for TVT-O, particularly when taking into consideration the base of surgical knowledge held by a surgeon who is being trained to use the product. The importance of the surgeon's experience and training are emphasized at the outset of the TVT-O IFU.

CONCLUSION:

Based on my extensive personal experience and my review of the vast clinical literature, it is my strongly held opinion that TVT and TVT-O have completely revolutionized the management of stress urinary incontinence and have resulted in extremely high satisfaction in the vast majority of my patients. Extrapolating this experience to the larger medical community, and in light of the high success rates reported in the medical literature, would reveal thousands if not millions of women whose lives have been reclaimed by a relatively simple 20-minute procedure that gets them back to work, to motherhood and to their lives within days. For frame of reference, as a young resident, I recall 2 or 3-hour surgeries, inpatient admissions with catheters, drains and suprapubic tubes, unfortunate failures and long recovery periods in order to offer a woman a cure of her stress incontinence. It would be a tragedy for women across the country to have to return to this kind of morbid and major surgery. Similarly, it would be unreasonable to expect women of all ages to simply endure the bothersome, embarrassing, burdensome and often debilitating consequences of stress urinary incontinence. TVT and TVT-O have proven to be the gold standard for the treatment of female stress incontinence. I am grateful to be able to practice urology at a time when TVT and TVT-O are not only available to me as a treatment option, but also widely studied as a device. And though no surgery is without complication or risk, the TVT and TVT-O are the best-studied options for the treatment of stress urinary incontinence that we have at this moment in time.

Dated: February 24, 2016



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